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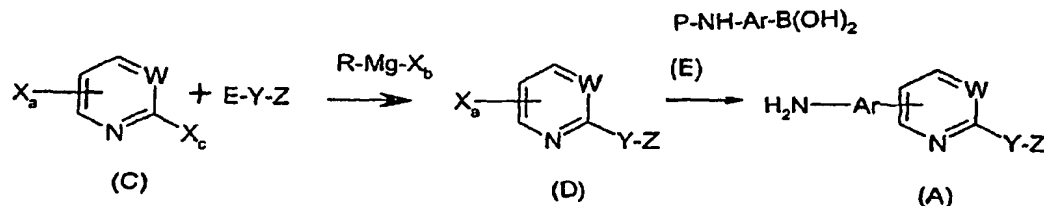
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(54) Title: NOVEL SYNTHESIS OF HETEROARYLAMINE INTERMEDIATE COMPOUNDS



(57) Abstract: Disclosed are novel 2-(5-halopyridyl) and 2-(5-halopyrimidinyl) magnesium halides, processes of making and their use in the efficient synthesis in their respective 5-halo-2-substituted pyridines and pyrimidines according to following scheme :

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Novel Synthesis of Heteroarylamine Intermediate Compounds

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APPLICATION DATA

This application claims benefit to US Provisional Application No. 60/206,327 filed May 23, 2000.

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FIELD OF INVENTION

The present invention relates to synthesis of heteroarylamine intermediate compounds.

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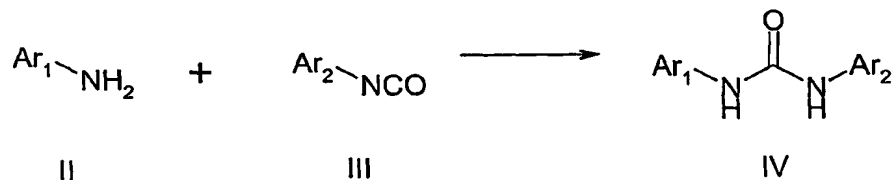
BACKGROUND OF THE INVENTION

Aryl- and heteroaryl-substituted ureas have been described as inhibitors of cytokine production. These inhibitors are described as effective therapeutics in cytokine-mediated diseases, including inflammatory and autoimmune diseases. Examples of such compounds are reported in WO 99/23091 and in WO 98/52558.

A key step in the synthesis of these compounds is the formation of the urea bond. Various methods have been reported to accomplish this. For example, as reported in the above references, an aromatic or heteroaromatic amine, II, may be reacted with an aromatic or heteroaromatic isocyanate III to generate the urea IV (Scheme I)

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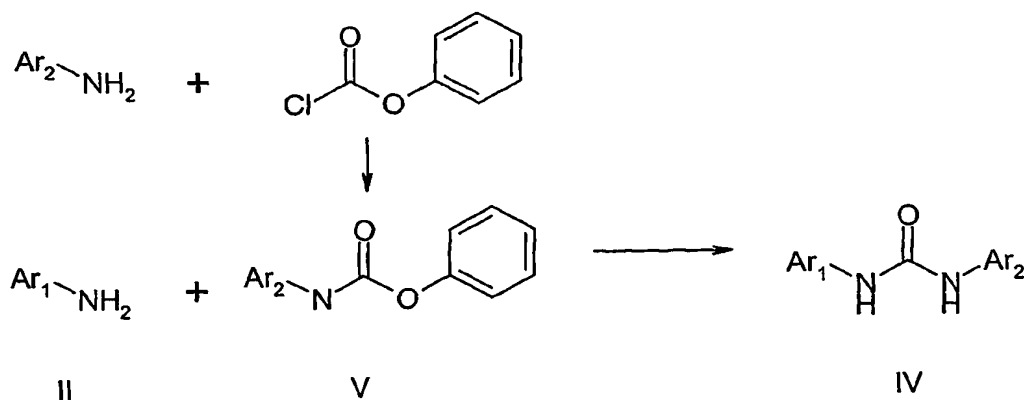
Scheme I



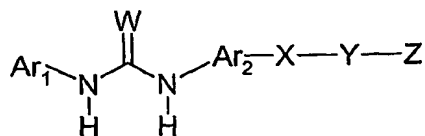
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If not commercially available, one may prepare the isocyanate III by reaction of an aryl or heteroaryl amine Ar_2NH_2 with phosgene or a phosgene equivalent, such as bis(trichloromethyl) carbonate (triphosgene) (P. Majer and R. S. Randad, *J. Org. Chem.* 1994, 59, 1937) or trichloromethyl chloroformate (diphosgene) (K. Kurita, T. Matsumura and Y. Iwakura, *J. Org. Chem.* 1976, 41, 2070) to form the isocyanate III, followed by reaction with Ar_1NH_2 to provide the urea. Other approaches to forming the urea reported in the chemical literature include reaction of a carbamate with an aryl or heteroaryl amine, (see for example B. Thavonekham, *Synthesis*, 1997, 1189 and T. Patonay et al., *Synthetic Communications*, 1996, 26, 4253) as shown in Scheme II below for a phenyl carbamate. US Patent Application no. 09/611,109 also discloses a process of making heteroaryl ureas by reacting particular carbamate intermediates with the desired arylamine.

Scheme II

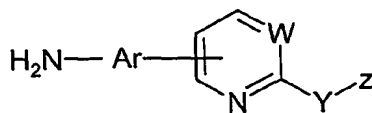


U.S. Application No. 09/505,582 and PCT/US00/03865 describe cytokine inhibiting ureas of formula (I).



(I)

An Ar_2NH_2 required to prepare preferred compounds described therein is illustrated as formula (A).



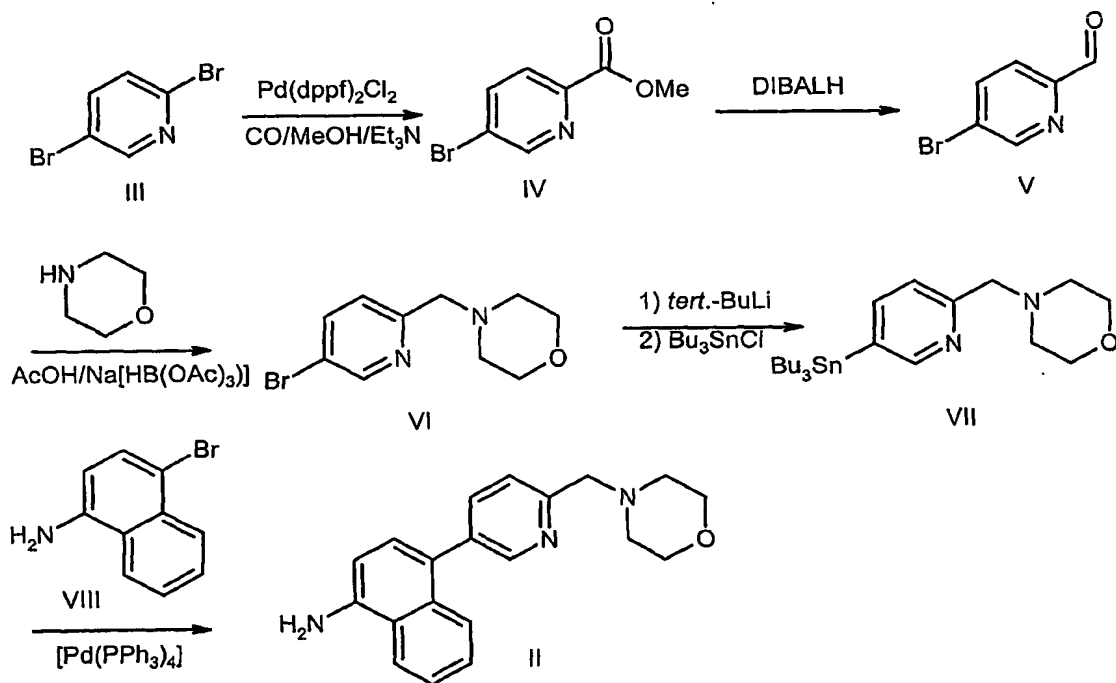
(A)

wherein W, Y, and Z are described below.

The synthesis of II, a preferred formula (A) intermediate was described in U.S.

Application No. 09/505,582 and PCT/US00/03865 and is illustrated in Scheme III.

Scheme III

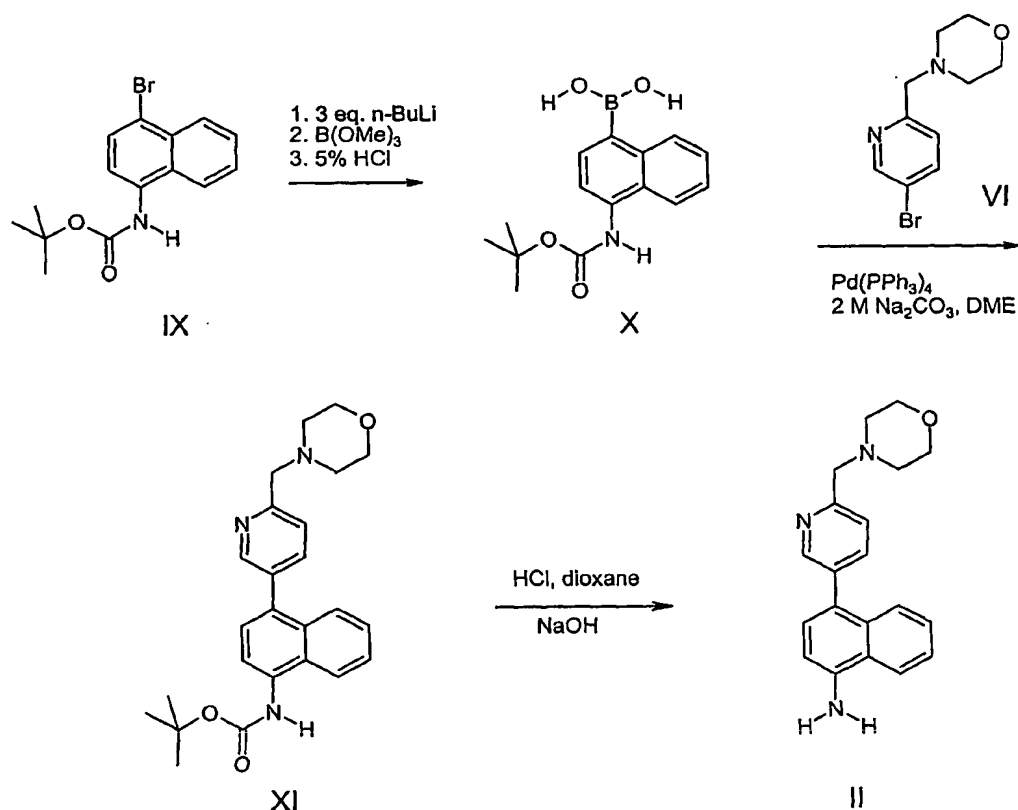


The synthesis begins with a palladium catalyzed carbonylation of 2,5-dibromopyridine (III) to provide ester IV in 55% yield. The reaction is run under pressure (80 psi CO) and must be monitored to minimize formation of the diester, an unwanted by-product. Reduction of IV with diisobutylaluminum hydride at -78 °C provides aldehyde V. This
5 is followed by reductive amination to give VI.

Intermediate VI is then converted to II by reaction with *t*-BuLi at -78 °C followed by tributyltin chloride to give tributylstannane VII, followed by palladium catalyzed Stille coupling with intermediate VIII to give II. Conversion of VI and analogous intermediates
10 to other intermediates of formula II via Suzuki coupling is also described in U.S. Application No. 09/505,582 and PCT/US00/03865 (Scheme IV). According to this method, intermediate IX is treated with *n*-BuLi followed by trimethylborate to give arylboronic acid X. Palladium catalyzed Suzuki coupling with VI provides XI, which is deprotected by treatment with acid to give II.

15

Scheme IV



This process is not well-suited for large-scale and commercial use for several reasons. One reaction (Scheme III) is run under high pressure (80 psi) and another at extreme temperature (-78°C). The yield of IV is only moderate and by-product formation requires a purification step. These factors, plus the cost of starting materials and reagents make this process too costly for commercial scale.

The preparation of 2-bromo-5-lithiopyridine via reaction of 2,5-dibromopyridine with *n*-BuLi at -100°C has been described (W.E.Parham and R.M.Piccirilli, *J.Org.Chem.*, **1977**, 42, 257). The selective formation of 2-bromo-5-pyridinemagnesium chloride via reaction with 2,5-dibromopyridine with *i*-PrMgCl at 0 °C - rt has also been reported (F. Trecourt *et al.*, *Tetrahedron Lett.*, **1999**, 40, 4339). In these cases, the metal-halogen exchange occurred exclusively at the 5 position of the pyridine ring. However, the syntheses of 5-

bromo-2-pyridinemagnesium chloride and 5-chloro-2-pyridinemagnesium chloride have not been reported previously.

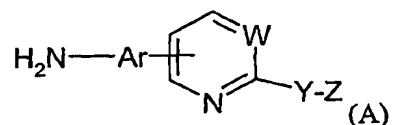
The preparation of a lithium intermediate 5-chloro-2-lithiopyridine from 2-bromo-5-chloropyridine, has been reported (U.Lehmann *et al.*, *Chem., Euro.J.*, 1999, 5, 854). However, this synthesis requires reaction with *n*-BuLi at -78°C . The preparation of the 5-bromo-2-lithiopyridine from 2,5-dibromopyridine was reported by X. Wang *et al.* (*Tetrahedron Letters*, 2000, 4335). However, the method requires cryogenic and high dilution conditions. The selectivity was also dependent on reaction time. It is not suitable for large scale synthesis.

The synthesis of the intermediate 5-bromo-2-iodopyridine by refluxing 2,5-dibromopyridine in HI has been reported (U.Lehmann, *ibid*). A process using milder conditions for preparing 2-iodopyridine from 2-chloro or 2-bromopyridine has been described (R.C. Corcoran and S.H. Bang, *Tetrahedon Lett.*, 1990, 31, 6757).

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel 2-(5-halopyridyl) and 2-(5-halopyrimidinyl) magnesium halides, novel methods of producing them, and to provide a novel method of using said halides in the efficient synthesis of their respective 5-halo-2-substituted pyridines and pyrimidines.

It also an object of the invention to provide a novel method of producing heteroaryl amines of the formula(A)

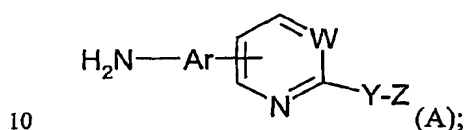


wherein Ar, W, Y and Z are described below, the heteroaryl amines are useful in the production of heteroaryl ureas as mentioned above.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention relates to a novel strategy for the synthesis of heteroarylamine compounds of the formula (A) which constitute the key component of pharmaceutically active compounds possessing a heteroaryl urea group.

The invention therefore provides for processes of making a compound of the formula (A)



wherein:

W is CR₃ or N, wherein R₃ is chosen from hydrogen, C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and -COR₄ wherein R₄ is chosen from C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and amino which is optionally independently di-substituted by C₁₋₅alkyl, and arylC₀₋₅alkyl; W is preferably CH or N,

Ar is chosen from phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indolinyl, benzothienyl, dihydrobenzothienyl, indanyl, indenyl and indolyl each being optionally substituted by one or more R₁ or R₂;

Y is chosen from a bond and a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, N, or S(O)_m and wherein Y is optionally independently

substituted with one to two oxo groups, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms;

wherein when Y is the carbon chain, the left side terminal atom of Y is a carbon (the
5 atom which is covalently attached to the heterocycle possessing W):

Z is chosen from:

aryl, heteroaryl chosen from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl,
10 imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl and pyranyl and heterocycle chosen from
tetrahydropyrimidinyl, cyclohexanonyl, cyclohexanolyl, 2-oxo- or 2-thio-5-aza-
bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl,
pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or
tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-
15 dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxidyl,
thiomorpholinyl sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl,
each of the aforementioned Z are optionally substituted with one to three halogen, C₁₋₆
alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxycarbonyl, aroyl, C₁₋₃acyl, oxo,
pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl,
20 nitrile, phenyl wherein the phenyl ring is optionally substituted with one to two halogen,
C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m wherein
the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, halogen or
mono- or di-(C₁₋₃ alkyl)amino;

25 or Z is optionally substituted with one to three amino or amino-C₁₋₃ alkyl wherein the N
atom is optionally independently mono- or di-substituted by aminoC₁₋₆alkyl, C₁₋₃alkyl,
arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m- or
arylC₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino
group is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

- 5 or Z is nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₆alkyl or C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy, nitrileC₁₋₄alkyl, C₁₋₆ alkyl-S(O)_m, aryl chosen from phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl each aryl being optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or nitrile, and phenyl-S(O)_m,
10 wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino;
- 15 R₁ and R₂ are independently chosen from:
a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl, C₁₋₃ alkyl-S(O)_m optionally partially or fully halogenated, or phenylsulfonyl;
20 m = 0, 1 or 2;

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₆alkoxy" is a C₁₋₆alkyl
25 with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

- Ac - acetyl;
30 DBA - dibenzylideneacetone;
DPPF - 1,1'-bis(diphenylphosphino)ferrocene;

DPPE - 1,2-bis(diphenylphosphino)ethane;
DPPB - 1,4-bis(diphenylphosphino)butane;
DPPP - 1,3-bis(diphenylphosphino)propane;
BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;
5 DME - ethylene glycol dimethylether;
DMSO - dimethyl sulfoxide;
DMF - *N,N*-dimethylformamide;
EtO - ethoxide;
ⁱPr - isopropyl;
10 ^tBu - tertbutyl;
THF- tetrahydrofuran;
RT or rt - room temperature;

The term "aroyl" as used in the present specification shall be understood to mean
15 "benzoyl" or "naphthoyl".

The term "aryl" as used herein shall be understood to mean aromatic carbocycle,
preferably phenyl and naphthyl, or heteroaryl.

20 The term "heterocycle", unless otherwise noted, refers to a stable nonaromatic 4-8
membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered
bicyclic heterocycle radical which may be either saturated or unsaturated. Each
heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms
selected from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom
25 of the cycle, which results in the creation of a stable structure. Unless otherwise stated,
heterocycles include but are not limited to, for example oxetanyl, pyrrolidinyl,
tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl,
tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene sulfoxidyl,
oxazoliny, thiazoliny, imidazoliny, tetrahydropyridiny, homopiperidinyl, pyrroliny,
30 tetrahydropyrimidinyl, decahydroquinoliny, decahydroisoquinoliny, thiomorpholiny,
thiazolidiny, dihydrooxaziny, dihydropyranyl, oxocanyl, heptacanyl, thioxanyl,

dithianyl or 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl.

The term "heteroaryl", unless otherwise noted, shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms
5 such as N,O and S. Unless otherwise stated, such heteroaryls include: pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl, tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzooxazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl,
10 benzo[1,3]dioxol-2-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl.

Terms which are analogs of the above cyclic moieties such as aryloxy or heteroaryl amine shall be understood to mean an aryl, heteroaryl, heterocycle as defined above
15 attached to it's respective functional group.

As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

20 The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine except as otherwise noted.

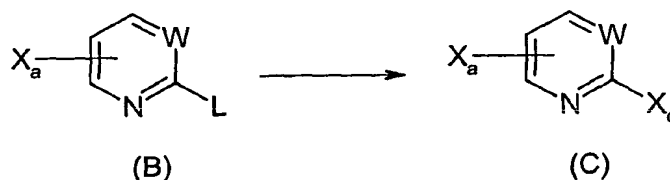
The compounds made by the novel processes of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are
25 not compounds made by processes contemplated by the invention.

In one embodiment of the invention there is provided a process of making the compounds of formula(A) as described hereinabove,

30 said process comprising:

a) synthesis of a compound of formula (C) from a compound of formula (B) via substitution with an appropriate halide X_c . When X_c is Br, methods known in the art may be utilized.

When X_c is I, the present invention provides a novel process for the substitution of the
 5 leaving group (L) with iodide. This was achieved by using the conditions of $R_x\text{COCl}$ or $(R_x\text{CO})_2\text{O}$ /metal iodide/solvent/heating ($25\text{ }^\circ\text{C}$ - $150\text{ }^\circ\text{C}$), wherein R_x is chosen from -C_{1-7} alkyl, -CF_{1-3} and -CCl_{1-3} ; the metal chosen from Na and K, and the solvent chosen from acetonitrile, acetone, DMSO, DMF and THF. Preferred conditions are AcCl and NaI in acetonitrile at $70\text{-}90\text{ }^\circ\text{C}$. The leaving group L is any suitable leaving group as will be
 10 appreciated by those skilled in the art, preferably L is chosen from Cl, Br, -OCOR_y and $\text{-OS(O)}_m\text{R}_y$, wherein R_y is aryl optionally substituted by C_{1-4} alkyl optionally halogenated, such as tolyl, or R_y is C_{1-4} alkyl optionally halogenated such as CF_3 and CCl_3 , L is more preferably chosen from Br and Cl.



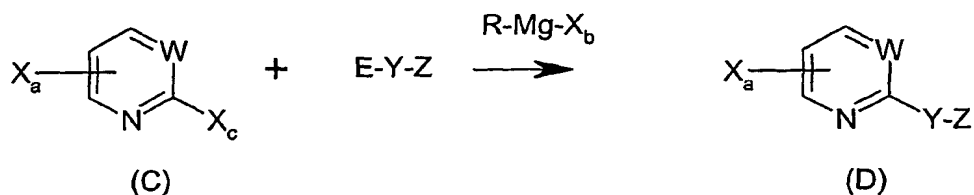
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X_a is chosen from Br and Cl, preferably Br;

X_c is I or Br, preferably I;

X_a is attached via the 4 or 5 ring position, preferably the 5 position.

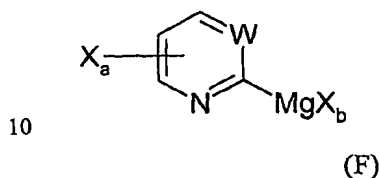
20 b) In a one pot process, reacting a compound of the formula(C) with a Grignard reagent R-Mg-X_b followed by the addition of an E-Y-Z compound wherein Y-Z is as defined above, said E-Y-Z component is further characterized as being an electrophilic derivative of Y-Z and being appropriate for Grignard reagent reactions as will be apparent to the skilled artisan, said reaction taking place in a suitable aprotic solvent at $-78\text{ }^\circ\text{C}$ to RT,
 25 preferably $0\text{ }^\circ\text{C}$ to RT for a reaction time of $\frac{1}{2}$ hour to 2 hours, preferably 1 hour, and isolating the compound of the formula (D);



wherein:

- 5 X_b is chosen from Br, Cl and I;
 R is aryl, C_{1-6} alkyl or C_{5-7} cycloalkyl;

As seen in Scheme V below, this one pot novel process step provides for the formation of the Grignard reagent Compound (F):

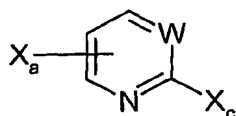


where a desirable selective formation was observed. For example the synthesis of 2-(5-halopyridyl)magnesium halides (e.g. 3 and 12) was achieved for the first time.

15

The process of making compounds of the formula(F) comprises:

reacting a compound of the formula(C)



(C)

- 20 with a magnesium reagent of the formula R-MgX_b ; said reaction taking place in a suitable aprotic solvent at -78°C to RT, for a reaction time of $\frac{1}{2}$ hour to 2 hours, producing the Grignard compound of the formula(F);
 and wherein

X_a is halogen selected from Br and Cl, and X_a is attached via the 4 or 5 ring position;

X_b is halogen chosen from Br, Cl and I;

X_c is I or Br;

W is CR_3 or N, wherein R_3 is chosen from hydrogen, C_{1-5} alkyl, C_{1-5} alkoxy, aryl C_{0-5} alkyl
 5 and $-COR_4$ wherein R_4 is chosen from C_{1-5} alkyl, C_{1-5} alkoxy, aryl C_{0-5} alkyl and amino
 which is optionally independently or di-substituted by C_{1-5} alkyl, and aryl C_{0-5} alkyl; W is
 preferably CH or N;

and

R is aryl, C_{1-6} alkyl or C_{5-7} cycloalkyl.

10

In a preferred embodiment there is provided a process for making a compound of the
 formula(F) as described above and wherein

W is CH;

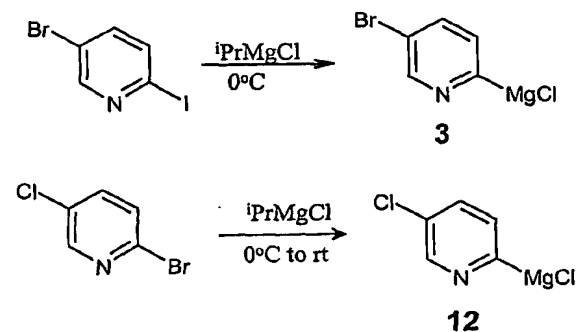
15 X_a is Br and attached at the 5 ring position;

X_c is I;

the temperature is 0 °C to RT; and

the reaction time is 1 hour.

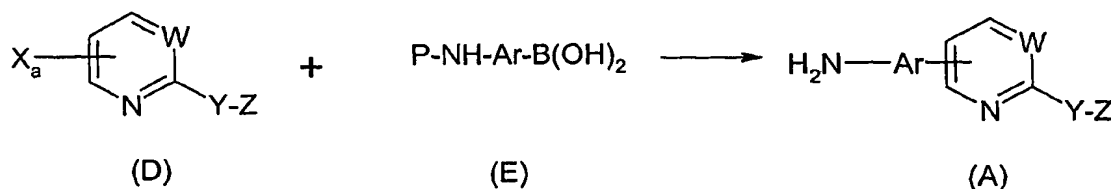
20 Non-limiting examples of this reaction proceeded with complete selectivity at the 2
 position in excellent yield:



In subsequent steps, the novel process of the invention further comprises:

25

c) reacting the compound of the formula(D) from step b) with an aryl boronic acid of the formula (E), in the presence of a catalyst chosen from nickel and palladium. Regarding the palladium(Pd) catalyst, non-limiting examples are Pd catalysts chosen from Pd(PPh₃)₂Cl₂, Pd(PPh₃)₄, PdCl₂(DPPE), PdCl₂(DPPB), PdCl₂(DPPP), PdCl₂(DPPF) and Pd/C; or the combination of a palladium source and an appropriate ligand, with the Pd source, for example, being chosen from PdCl₂, Pd(OAc)₂, Pd₂(DBA)₃, Pd(DBA)₂, and with the ligand being chosen from PPh₃, DPPF, DPPP, DPPE, DPPB, P(*o*-tolyl)₃, P(2,4,6-trimethoxyphenyl)₃, AsPh₃, P(^tBu)₃, BINAP, and those bound to solid supports that are mimics of the aforementioned ligands, preferably PdCl₂ and PPh₃. Regarding the nickel(Ni) catalyst, examples of nickel (Ni) catalyst are those chosen from Ni(PPh₃)₂Cl₂, Ni(PPh₃)₄, NiCl₂(DPPE), NiCl₂(DPPB), NiCl₂(DPPP), NiCl₂(DPPF) and Ni/C; or the combination of a Ni source and an appropriate ligand, with the Ni source being NiCl₂, and with the ligand being chosen from PPh₃, DPPF, DPPP, DPPE, DPPB, P(*o*-tolyl)₃, P(2,4,6-trimethoxyphenyl)₃, AsPh₃, P(^tBu)₃, BINAP, and those bound to solid supports that are mimics of the aforementioned ligands. This reaction takes place in a suitable solvent such as ethylene glycol dimethyl ether (DME), THF, toluene, methylene chloride or water, preferably DME, at 0 °C to 150 °C, preferably 25 °C to 100 °C, for a period of 1 to 24 hours preferably about 15 hours,



20

wherein P in the formula(E) is an amino protecting group such as Boc, and subsequently removing said protecting group under suitable conditions to produce a compound of the formula(A).

25

In a preferred embodiment of the invention there is provided a novel process of making compounds of the formula(A) as described above and wherein:

W is CH;

Ar is chosen from naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, indanyl, indenyl and indolyl each being
5 optionally substituted by one or more R₁ or R₂ groups;

Y is chosen from:

a bond and

10 a C₁₋₄ saturated or unsaturated carbon chain wherein one of the carbon atoms is optionally replaced by O, N, or S(O)_m and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms; wherein when Y is the carbon chain, the left side terminal atom of Y is a carbon (the atom which is covalently attached to the heterocycle possessing W):

15

Z is chosen from:

phenyl, pyridiny, pyrimidiny, pyridaziny, pyraziny, imidazolyl, furanyl, thienyl,
20 dihydrothiazolyl, dihydrothiazolyl sulfoxidyl, pyranyl, pyrrolidiny which are optionally substituted with one to three nitrile, C₁₋₃ alkyl, C₁₋₃ alkoxy, amino or mono- or di-(C₁₋₃ alkyl)amino;

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl,
25 morpholiny, thiomorpholiny, thiomorpholiny sulfoxidyl, piperidiny, piperidinonyl, piperaziny, tetrahydropyrimidonyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl which are optionally substituted with one to three nitrile, C₁₋₃ alkyl, C₁₋₃ alkoxy, amino or mono- or di-(C₁₋₃ alkyl)amino;

30

nitrile, C₁₋₆ alkyl-S(O)_m, halogen, C₁₋₄ alkoxy, amino, mono- or di-(C₁₋₆ alkyl)amino and di-(C₁₋₃ alkyl)aminocarbonyl;

In a more preferred embodiment of the invention there is provided a novel process of making compounds of the formula(A) as described immediately above and wherein:

Ar is naphthyl;

Y is chosen from:

a bond and

a C₁₋₄ saturated carbon chain wherein the left side terminal atom of Y is a carbon (the atom which is covalently attached to the heterocycle possessing W) and one of the other carbon atoms is optionally replaced by O, N or S and wherein Y is optionally independently substituted with an oxo group;

Z is chosen from:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, dihydrothiazolyl, dihydrothiazolyl sulfoxide, pyranyl and pyrrolidinyl which are optionally substituted with one to two C₁₋₂ alkyl or C₁₋₂ alkoxy;

tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl and tetrahydropyrimidinonyl which are optionally substituted with one to two C₁₋₂ alkyl or C₁₋₂ alkoxy; and C₁₋₃ alkoxy;

In yet a more preferred embodiment of the invention there is provided a novel process of making compounds of the formula(A) as described immediately above and wherein:

Ar is 1-naphthyl wherein the NH₂ is at the 4 position;

Y is chosen from:

a bond, -CH₂-, -CH₂CH₂- and -C(O)-;

In an ultimately preferred embodiment of the invention there is provided a novel process of making compounds of the formula(A) as described immediately above and wherein:

5 Y is

-CH₂;

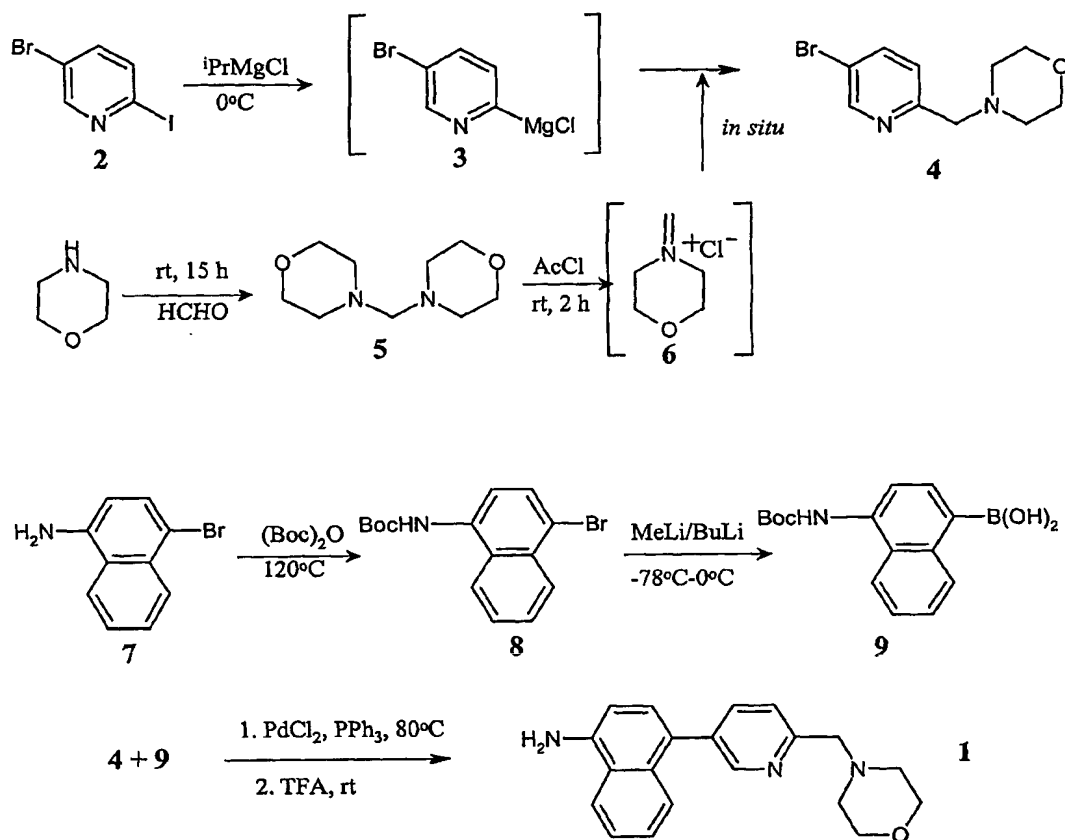
 Z is morpholinyl;

10 Formation of the reaction intermediate (E) can be accomplished by first protecting an aryl-amine followed by boronic acid formation through a sequence of metal-bromine exchange, quenching with trialkylborate and hydrolysis, as can be seen in Scheme V in the conversion of 7 to 9. Compounds of the formula (E) possessing other desired Ar can be accomplished without undue experimentation by variations apparent to those of ordinary skill in the art in view of the teachings in this specification and the state of the
15 art.

 A desirable novel feature of the process of the invention is the selective formation of a 2-(5-halopyridyl) or 2-(5-halopyrimidinyl) magnesium halides, preferably 2-(5-halopyridyl) magnesium halides (e.g. 3 and 12, *vide infra*), and their subsequent reactions with the
20 *situ* generated E-Y-Z electrophiles. Below in Scheme 1, the addition of 2-(5-halopyridyl) magnesium halide 3 to the immonium salt 6 was carried out without the isolation of the immonium salt.

 A non-limiting example for a compound of the formula (A) is the amine 1 shown in
25 Scheme V.

Scheme V

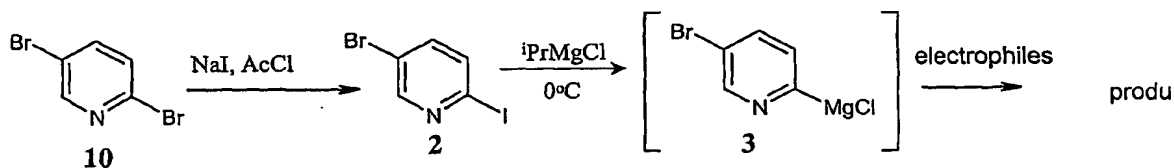


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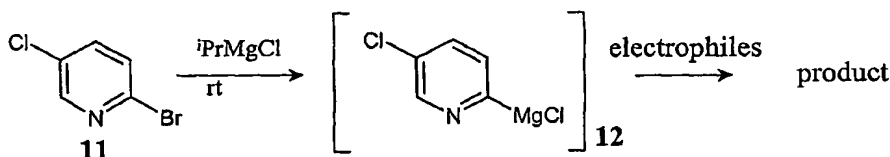
Reaction intermediate (**2**) with a generic formula (B) above can be obtained as exemplified in Scheme VI below. Addition of a copper catalyst may be required for transformations involving certain types of electrophiles, for example the alkylation reaction of the Grignard intermediate with various alkyl halides and epoxides.

10

Scheme VI



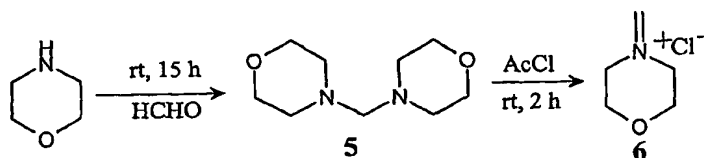
OR



5

Examples of appropriate electrophiles are shown in the table below. Methods of making Y-Z electrophilic derivatives are within the skill in the art. Y component in Y-Z is a derivative of the Y of the formula (A) of the final product upon the addition of the electrophile to the Grignard intermediate. Products may be further derivatized to achieve the desired Y-Z. Such further transformations are within the skills in the art. A non-limiting example is shown below for a preferred embodiment of Z in the formula (A), i.e., the morpholino immonium salt **6**. Reference in this regard may be made to Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, 53, 2941; Sliwa, H.; Blondeau, D. *Heterocycles* **1981**, 16, 2159;

15



In this example, E-Y-Z is compound **6**, wherein morpholinyl represents Z and Y is $-\text{CH}_2-$ in the final product.

As described above, any electrophile represented by Y, possessing a Z component and compatible with Grignard type reactions are contemplated to be within the scope of the invention. Additional non-limiting examples of E-Y-Z are:

5



wherein E-Y is an aldehyde such as Z-CHO, thus Y in Formula (A) would be -CH(OH)-.



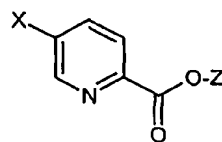
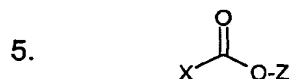
10 wherein NRR represent any of the above-listed Z amine moieties or heterocycles possessing a nitrogen heteroatom and Y can be alkylene such as -CH₂-, X is a countervalent anion.



15 wherein E-Y is a branched or unbranched alkoxy possessing a halogen atom X and further linked to Z, such as ClCH₂-O-Z.



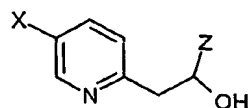
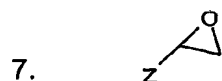
20 wherein E-Y is a C₁₋₄acyl halide such as formylchloride, NRR' represents any of the above-listed Z amine moieties, or heterocycles possessing a nitrogen heteroatom. LG is an appropriate leaving group such as halogens. (see: Katritzky *et al.*, *J. Chem. Res.* 1999, 3, 230.)



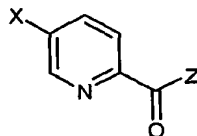
wherein E-Y is a haloester moiety such as chloroformate. X is an appropriate leaving
 5 group such as halogens or alkoxy groups. (see: Satyanarayana *et al.*, *Synth. Commun.*
 1990, 20 (21), 3273.)



10 wherein an appropriate Z-Y is substituted by halogen X, preferably iodine, such as CH_3I .

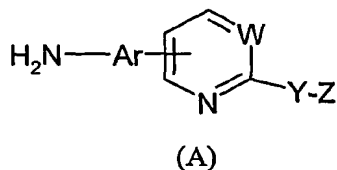


15 Addition of an appropriate Z attached to a reactive epoxide provides the hydroxy
 intermediate which is further derivatized to the desired Y component.



20 Acylation wherein Y is an acyl attached to Z may be accomplished via the appropriate
 acylation reagent such as the ester shown above wherein -OR is a known leaving group.

In another embodiment of the invention there is provided a process of making the
 compounds of formula(A):



wherein Ar and W are as described above;

5

and wherein for the formula(A):

Y is -CH₂-; and

10 Z is chosen from:

heterocycle chosen from morpholinyl, thiomorpholinyl, piperidinyl and pyrrolidinyl
each of the aforementioned Z are optionally substituted with one to three halogen, C₁₋₆
alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxycarbonyl, aroyl, C₁₋₃acyl, oxo,
pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl,
15 nitrile, phenyl wherein the phenyl ring is optionally substituted with one to two halogen,
C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m wherein the phenyl
ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or di-(C₁₋₃
alkyl)amino;

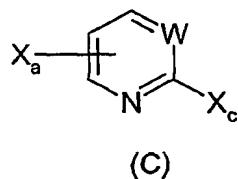
20 or Z is optionally substituted with one to three one to three amino or amino-C₁₋₃ alkyl
wherein the N atom is optionally independently di-substituted by aminoC₁₋₆alkyl, C₁₋₃
alkyl, arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m-
or arylC₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino
group is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

25 or Z is optionally substituted with one to three aryl or heterocycle as hereinabove
described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or
C₁₋₆ alkoxy;

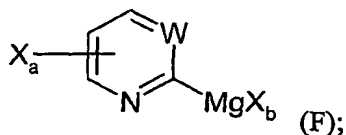
- or Z is amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₆alkyl or C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy, nitrileC₁₋₄alkyl, C₁₋₆ alkyl-S(O)_m, aryl chosen from phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl each
- 5 aryl being optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or nitrile, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino;

- 10 said reaction comprising:

reacting a compound of the formula(C)



- with a magnesium reagent of the formula R-MgX_b; said reaction taking place in a suitable
- 15 aprotic solvent at -78 °C to RT, for a reaction time of ½ hour to 2 hours producing the Grignard compound(F):

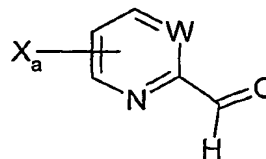


wherein

- X_a is halogen selected from Br and Cl, and X_a is attached to the ring via the 4 or 5
- 20 position;
- X_b is halogen chosen from Br, Cl and I;
- X_c is I or Br;
- W is CH, CCH₃ or N; and
- R is aryl, C₁₋₆alkyl or C₅₋₇cycloalkyl;

25

subsequently reacting the Grignard compound from the prior step with a N,N-

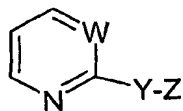


dialkylformamide such as DMF to form an aldehyde:

and

isolating the aldehyde;

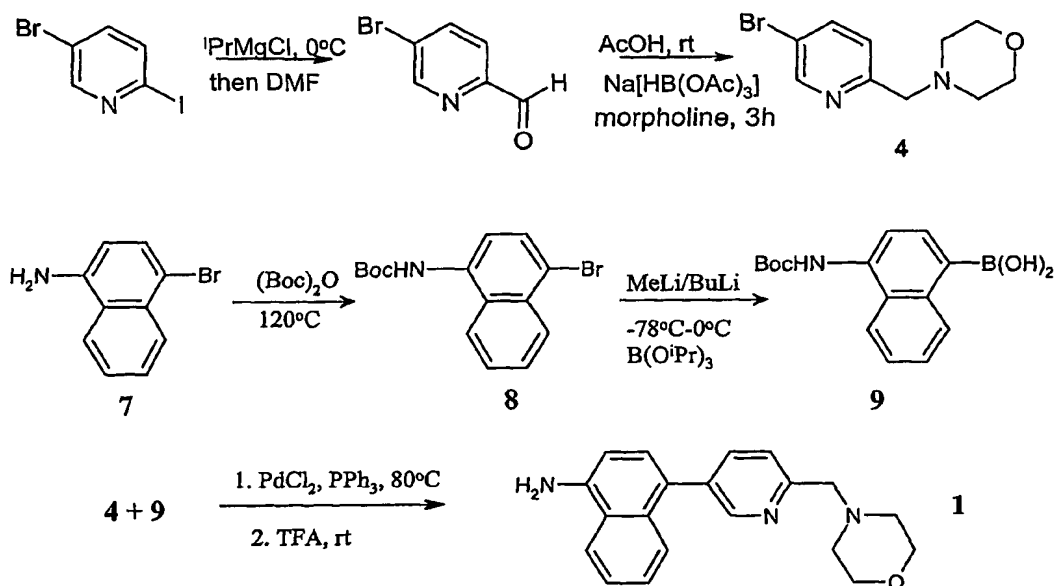
- 5 reacting the aldehyde with an appropriate Z group under nucleophilic addition conditions



to provide the compound (D). This transformation is within the skill in the art and involves reacting of the aldehyde and the appropriate Z component under acidic conditions such as HCl, AcOH, H₂SO₄ etc, preferably AcOH, in a suitable solvent such as THF, methylene chloride, 1,2-dichloroethane, preferably 1,2-dichloroethane for
 10 0.5-5 h (preferably 2 h) at about RT followed by in situ reduction for 0.5-5 h (preferably 2 h) to provide the product (D).

Subsequent addition of the NH₂-Ar compound can be done as described hereinabove, to provide the final product compound of the formula(A) as described above in this
 15 embodiment of the invention. A non-limiting example of this embodiment of the invention is shown in Scheme VII.

Scheme VII



In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

5

SYNTHETIC EXAMPLES

10

Example 1

Synthesis of 5-bromo-2-iodopyridine from 2,5-dibromopyridine:

2,5-Dibromopyridine (100 g) was suspended in acetonitrile (500 mL) at rt. NaI (94 g) and AcCl (45 mL) were added and the reaction was then gently refluxed for 3 h. An aliquot was analyzed by ^1H NMR and MS and the reaction was about 80% complete. The reaction was cooled to rt and quenched with a few mL of water and then K_2CO_3 aqueous solution to pH 8. EtOAc (1.5 L) was added to extract the organic materials. The organic layer was washed with saturated NaHSO_3 solution, the brine, and then dried over MgSO_4 . Concentration gave crude material that was subjected to the same conditions for about 3 h

at which time ^1H NMR showed that the reaction was greater than 97% complete. The same workup provided the crude material. The crude crystals were washed twice with CH_3CN and dried in the oven. The yield was 95 g.

^1H NMR (CDCl_3 , 400 MHz) δ 8.44 (s, 1H), 7.60 (d, $J=8.26$ Hz, 1H), 7.44 (d, $J=8.25$ Hz, 1H).

Example 2

Synthesis of 5-bromo-2-formylpyridine from 5-bromo-2-iodopyridine via the Grignard intermediate:

In a 22 L 3-neck round bottomed flask equipped with a mechanical stirrer, 1 kg (3.52 mol) of 2-iodo-5-bromopyridine was dissolved in 5 L of THF. The solution was cooled to about -15 to -10 $^\circ\text{C}$. 1.9 L (2 M, 380 mol, 1.08 eq) of $^i\text{PrMgCl}$ was added at a rate to keep the internal temperature below 0 $^\circ\text{C}$. The reaction mixture became a brown suspension. After the reaction mixture was stirred between -15 to 0 $^\circ\text{C}$ for 1 h, 400 mL (5.16 mol, 1.5 eq) of DMF was added at a rate to keep the internal temperature below 0 $^\circ\text{C}$. After stirring at this temperature for 30 min, the cooling bath was removed and the reaction was allowed to warm to room temperature over 1 h. The reaction mixture was then cooled to 0 $^\circ\text{C}$ and 4.0 L (7.74 mol, 2.2 eq) of 2 N HCl was added at a rate to keep the internal temperature below 25 $^\circ\text{C}$. The mixture was stirred for 30 min, then pH was raised from 1 to a pH 6-7 by adding about 150 mL of 2 N NaOH. The layers were separated and the THF layer was concentrated to give dark brown wet solids. The aqueous layer was extracted with 3 L of CH_2Cl_2 . The CH_2Cl_2 layer was used to dissolve the residue obtained from the THF layer, the resulting solution was washed with water (2 x 2 L), dried by stirring with MgSO_4 (400 g) for 30 min, and filtered. Concentration of the filtrate to dryness gave 583 g of the desired aldehyde as brownish-yellow solids (89% yield after air drying).

^1H NMR (CDCl_3 , 400 MHz) δ 10.04 (d, $J=0.68$ Hz, 1H), 8.86 (t, $J=0.52$ Hz, 1H), 8.02 (dt, $J=8.20, 0.68$ Hz, 1H), 7.85 (d, $J=8.48$ Hz, 1H).

Example 3

Synthesis of 5-bromo-2-(4-morpholinylmethyl)pyridine from 5-bromo-2-iodopyridine via the Grignard intermediate:

5 To a solution of bis(1-morpholinyl)methane (130 mg) in THF (3 mL) at rt was added acetyl chloride (45 mL). The reaction was stirred for 1 h and cooled to 0 °C.

In another flask, 5-bromo-2-iodopyridine (130 mg) was dissolved in THF (3 mL) at –40°C. The solution was treated with ⁱPrMgCl (2 M in THF, 0.39 mL) at the same temperature for 15 min. Then the Grignard solution was cannulated into the immonium salt suspension generated above at 0 °C. After the addition, the reaction mixture was stirred at rt for 1h and quenched with saturated NH₄Cl solution. Extraction with CH₂Cl₂, drying over MgSO₄, filtration and concentration gave a crude oil. This was further purified by column chromatography to afford the product in about 50 % yield.

¹H NMR (CDCl₃, 400 MHz) δ 8.60 (s, 1H), 7.76 (d, *J*= 8.24 Hz, 1H), 7.32 (d, *J*= 8.64 Hz, 1H), 3.72 (m, 4H), 3.59 (s, 2H), 2.48 (m, 4H).

Example 4

Synthesis of 5-bromo-2-(4-morpholinyl)methylpyridine from 5-bromo-2-formylpyridine

20 To a solution of 500 g (2.688 moles) aldehyde in a 5 L of 1,2- dichloroethane at room temperature was added morpholine (1.15 eq, 3.09 moles, 269 ml) in one portion. The reaction temperature went up to 29 °C. After stirring the reaction mixture for 15 min, acetic acid (2.1 eq, 5.6 moles, 323 mL) was added in one portion. The temperature rose to 31 °C. It was stirred for 1.5 h at room temperature. Sodium triacetoxymethylborohydride (1.06 eq, 2.85 moles, 604 g) was added in 100 g portions every 10 min. The temperature was maintained between 35 °C and 46 °C by gentle cooling. It was stirred for an additional 2 h.

30 The reaction mixture was quenched with 4 N HCl keeping the temperature below 15 °C. At the end of addition, the pH of aqueous phase was between 0 and 1 (~2200 mL). The organic phase was separated and discarded. The aqueous phase was basified with 9 N

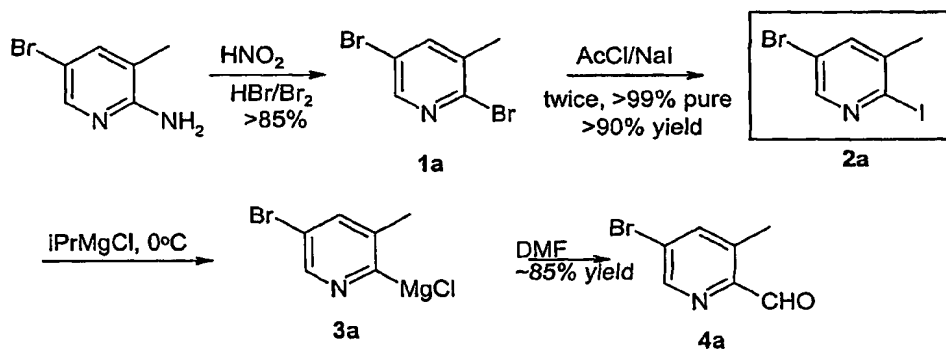
NaOH (~740 g NaOH) to pH ~9.5 keeping the internal temperature below 15 °C. The product was extracted with methylene chloride. Evaporation of the solvent gave pure amine (660 g, 2.57 moles).

5

Example 5**Synthesis of 5-Bromo-3-methyl-2-pyridinecarboxaldehyde**

10

An example of the synthesis of a compound of formula (F) in which W is CR₃ (R₃ = methyl), and subsequent reaction with an electrophile is provided below and illustrated in Scheme VIII.

Scheme VIII

15

20

2,5-Dibromo-3-picoline is commercially available or may be prepared from 2-amino-5-bromo-3-methylpyridine by standard diazotization followed by bromination in Br₂/HBr. Acetyl chloride (0.68 mol, 52.7 mL) was added to a stirring solution of 2,5-dibromo-3-picoline (0.45 mol, 113 g) in acetonitrile (600 mL) followed by sodium iodide (1.66 mol, 250 g) and the reaction mixture was gently refluxed for 18 h. The cooled reaction mixture was filtered and the solid was washed with acetonitrile until colorless. It was suspended in methylene chloride and treated with aq. Na₂CO₃ until the pH was 10-11. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to give a brown oil. It was subjected to iodination a second time as above (reflux time 6 h). A dark brown oil was obtained using the same work-up as above. A solution of this oil in hexane was treated with charcoal, filtered and concentrated to give a light brown oil. It slowly solidified on standing to give 5-bromo-2-iodo-3-methylpyridine as a light brown solid (95.0 g, 0.32 mol). Yield: 70%.

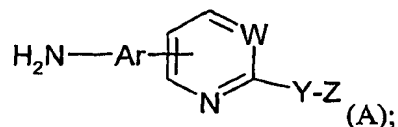
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2-Iodo-5-bromo-3-methylpyridine (250 mg) was dissolved in THF (4.0 mL). The solution was cooled to 0 °C. ⁱPrMgCl (2 M in THF, 0.5 mL) was added at a rate to keep the internal temperature below 5 °C. After the reaction mixture was stirred at 0 °C for 1 h, DMF (0.13 mL) was added at 0 °C. After stirring at this temperature for 30 min, the cooling bath was removed and the reaction was allowed to warm to room temperature over 1 h. The reaction mixture was hydrolyzed by a saturated aqueous NH₄Cl solution. Then the aqueous layer was extracted with CH₂Cl₂. The CH₂Cl₂ layer was dried over MgSO₄ and concentrated to give the desired aldehyde as a brownish-yellow solid (80% yield).

25

What is claimed is:

1. A process of making a compound of the formula(A)



5

wherein:

W is CR₃ or N, wherein R₃ is chosen from hydrogen, C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and -COR₄ wherein R₄ is chosen from C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and amino
10 which is optionally independently or di-substituted by C₁₋₅alkyl, and arylC₀₋₅alkyl;

Ar is chosen from:

phenyl, naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indoliny,
15 benzothienyl, dihydrobenzothienyl, indanyl, indenyl and indolyl each being optionally substituted by one or more R₁ or R₂;

Y is chosen from

a bond, C₁₋₄ saturated or unsaturated branched or unbranched carbon chain optionally
20 partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, N, or S(O)_m and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms; wherein when Y is the carbon chain, the left side terminal atom of Y is a carbon;

25

Z is chosen from:

aryl, heteroaryl chosen from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl,
30 imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl and pyranyl, heterocycle chosen from

- tetrahydropyrimidonyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranlyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxidyl, thiomorpholinyl sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl, each of the aforementioned Z are optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxycarbonyl, aroyl, C₁₋₃acyl, oxo, pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl, nitrile, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, halogen or mono- or di-(C₁₋₃ alkyl)amino;
- or Z is optionally substituted with one to three amino or amino-C₁₋₃ alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC₁₋₆alkyl, C₁₋₃alkyl, arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m- or arylC₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
- or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
- or Z is nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₆alkyl or C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy, nitrileC₁₋₄alkyl, C₁₋₆ alkyl-S(O)_m, aryl chosen from phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranlyl each aryl being optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or nitrile, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino;

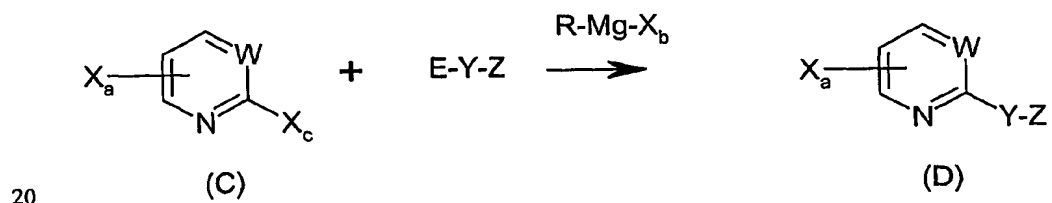
R_1 and R_2 are independently chosen from:

- a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy, each being optionally partially or fully
 5 halogenated, halogen, methoxycarbonyl, C_{1-3} alkyl-S(O) $_m$ optionally partially or fully halogenated, or phenylsulfonyl;

$m = 0, 1$ or 2 ;

10 said process comprising:

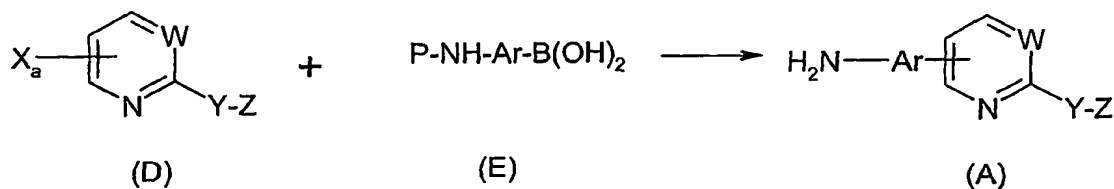
- i) in a one pot process, reacting a compound of the formula (C) with a Grignard reagent $R-Mg-X_b$ followed by the addition of an $E-Y-Z$ compound wherein $Y-Z$ is as defined
 15 above, said $E-Y-Z$ component is further characterized as being an electrophilic derivative of $Y-Z$, said reaction taking place in a suitable aprotic solvent at $-78^\circ C$ to RT , for a reaction time of $\frac{1}{2}$ hour to 2 hours, and isolating the compound of the formula (D);



wherein:

- X_a is chosen from Br and Cl, and attached to the ring at the 4 or 5 position;
 25 X_b is chosen from Br, Cl and I;
 X_c is chosen from I and Br;
 R is chosen from aryl, C_{1-6} alkyl and C_{5-7} cycloalkyl;

- ii) reacting the compound of the formula(D) from step a) with an aryl boronic acid of the formula (E) in the presence of a catalyst chosen from nickel, palladium and a combination of a palladium source and an appropriate ligand, in a suitable solvent at 0 °C to 150 °C, for about 1 to 24 hours:



- wherein P in the formula(E) is an amino protecting group, and subsequently removing said protecting group under suitable conditions to produce a compound of the formula(A).

2. The process according to claim 1 wherein W is CH or N.
3. The process according to claim 2 wherein:

- in step i) :
- X_a is Br attached to the 5 position of the ring;
- X_c is I;
- the reaction temperature is preferably 0 °C to RT;
- the reaction time is 1 hour;
- R is C₁₋₆alkyl;

- in step ii):
- the catalyst is a palladium catalyst chosen from Pd(PPh₃)₂Cl₂, Pd(PPh₃)₄, PdCl₂(DPPE), PdCl₂(DPPB), PdCl₂(DPPP), PdCl₂(DPPF) and Pd/C;
- or the catalyst is a combination of a palladium source and an appropriate ligand wherein the Pd source is chosen from PdCl₂, Pd(OAc)₂, Pd₂(DBA)₃ and Pd(DBA)₂; and wherein

the ligand is chosen from PPh_3 , DPPF, DPPP, DPPE, DPPB, $\text{P}(o\text{-tolyl})_3$, $\text{P}(2,4,6\text{-trimethoxyphenyl})_3$, AsPh_3 , $\text{P}(\text{t-Bu})_3$, and BINAP;

the temperature is 25°C to 100°C ;

the reaction time is about 15 hours;

- 5 the solvent is chosen from DME, THF, toluene, methylene chloride and water.

4. The process according to claim 3,

in step i) R is isopropyl;

- 10 in step ii):

the catalyst is a combination of a palladium source and an appropriate ligand wherein the palladium source is PdCl_2 and the ligand is PPh_3 , and

the solvent is DME.

- 15 5 The process according to claim 4 wherein:

W is CH_2 ;

Ar is chosen from naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, indanyl, indenyl and indolyl each being

- 20 optionally substituted by one or more R_1 or R_2 groups;

Y is chosen from:

a bond and

- 25 a C_{1-4} saturated or unsaturated carbon chain wherein one of the carbon atoms is optionally replaced by O, N, or $\text{S}(\text{O})_m$ and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms; wherein when Y is the carbon chain, the left side terminal atom of Y is a carbon (the atom which is covalently attached to the heterocycle possessing W)

30

Z is chosen from:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, furanyl, thienyl, dihydrothiazolyl, dihydrothiazolyl sulfoxidyl, pyranyl, pyrrolidinyl which are optionally substituted with one to three nitrile, C₁₋₃ alkyl, C₁₋₃ alkoxy, amino or mono- or di-(C₁₋₃ alkyl)amino;
5 alkyl)amino;

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl, tetrahydropyrimidinonyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, 10 pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl and tetramethylene sulfonyl which are optionally substituted with one to three nitrile, C₁₋₃ alkyl, C₁₋₃ alkoxy, amino or mono- or di-(C₁₋₃ alkyl)amino;

nitrile, C₁₋₆ alkyl-S(O)_m, halogen, C₁₋₄ alkoxy, amino, mono- or di-(C₁₋₆ alkyl)amino and 15 di-(C₁₋₃ alkyl)aminocarbonyl.

6. The process according to claim 5 wherein:

20 Ar is naphthyl;

Y is chosen from:

a bond and

a C₁₋₄ saturated carbon chain wherein the left side terminal atom of Y is a carbon (the 25 atom which is covalently attached to the heterocycle possessing W) and one of the other carbon atoms is optionally replaced by O, N or S and wherein Y is optionally independently substituted with an oxo group;

Z is chosen from:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, dihydrothiazolyl, dihydrothiazolyl sulfoxide, pyranyl and pyrrolidinyl which are optionally substituted with one to two C₁₋₂ alkyl or C₁₋₂ alkoxy;

- 5 tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl and tetrahydropyrimidinyl which are optionally substituted with one to two C₁₋₂ alkyl or C₁₋₂ alkoxy; and C₁₋₃ alkoxy.

10

7. The process according to claim 6 wherein:

Ar is 1-naphthyl wherein the NH₂ is at the 4-position; and

15

Y is chosen from:

a bond, -CH₂-, -CH₂CH₂- and -C(O)-.

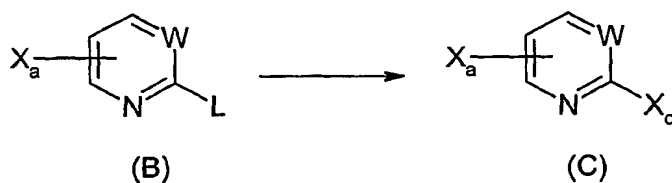
8. The process according to claim 7 wherein:

20

Y is -CH₂-; and

Z is morpholinyl.

- 25 9. A process of making a compound formula (C) from a compound of formula (B): said process comprising:
reacting a compound of the formula(B) with R_xCOCl or (R_xCO)₂O and a metal iodide in a suitable solvent at a temperature of 25 °C to 150 °C, wherein R_x is chosen from -C₁₋₇ alkyl, -CF₁₋₃ and -CCl₁₋₃;



X_a is chosen from Br and Cl and X_a is attached via the 4 or 5 ring position;

X_c is chosen from I and Br;

- 5 W is CR_3 or N, wherein R_3 is chosen from hydrogen, C_{1-5} alkyl, C_{1-5} alkoxy, aryl C_{0-5} alkyl and $-COR_4$ wherein R_4 is chosen from C_{1-5} alkyl, C_{1-5} alkoxy, aryl C_{0-5} alkyl and amino which is optionally independently or di-substituted by C_{1-5} alkyl, and aryl C_{0-5} alkyl;
and

L is a suitable leaving group.

10

10. The process according to claim 9 wherein W is CH, CCH_3 or N.

11. The process according to claim 10 wherein

X_a is Br attached at the 5 ring position;

- 15 X_c is I;

L is chosen from Cl, Br, $-OCOR_y$ and $-OS(O)_mR_y$, wherein R_y is aryl optionally substituted by C_{1-4} alkyl optionally halogenated, or R_y is C_{1-4} alkyl optionally halogenated;
the metal is chosen from Na and K;

and the solvent is chosen from acetonitrile, acetone, DMSO, DMF and THF.

20

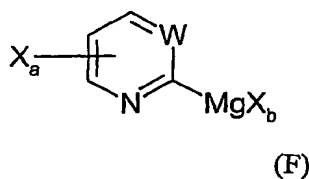
12. The process according to claim 11 wherein:

the compound of formula(B) is reacted with AcCl and NaI in acetonitrile at 70-90 °C; and

L is chosen from Br and Cl.

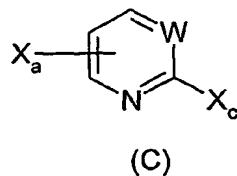
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13. A process of making a Grignard compound of the formula(F):



5 said process comprising:

reacting a compound of the formula(C)



10 with a magnesium reagent of the formula R-MgX_b; said reaction taking place in a suitable aprotic solvent at -78 °C to RT, for a reaction time of ½ hour to 2 hours, producing the Grignard compound of the formula(F);

and wherein

X_a is chosen from Br and Cl, and X_a is attached via the 4 or 5 ring position;

X_b is chosen from Br, Cl and I;

15 X_c is chosen from I and Br;

W is CR₃ or N, wherein R₃ is chosen from hydrogen, C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and -COR₄ wherein R₄ is chosen from C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and amino which is optionally independently or di-substituted by C₁₋₅alkyl, and arylC₀₋₅alkyl; W is preferably CH or N; and

20 R is chosen from aryl, C₁₋₆alkyl and C₅₋₇cycloalkyl.

14. The process according to claim 13 wherein W is CH, CCH₃, or N.

25 15. The process according to claim 14, wherein

W is CH;

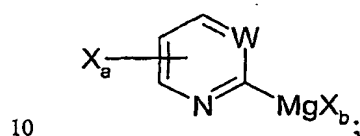
X_a is Br and attached at the 5 ring position;

X_c is I;

the temperature is 0 °C to RT; and

5 the reaction time is 1 hour.

16. A compound of the formula:



X_a is chosen from Br and Cl, and X_a is attached via the 4 or 5 ring position;

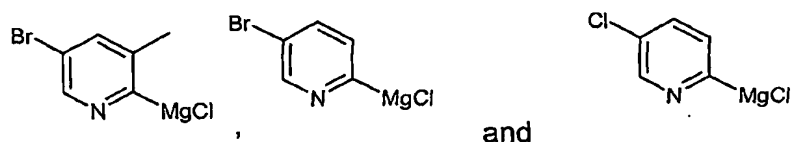
X_b is chosen from Br, Cl and I; and

15 W is CR₃ or N, wherein R₃ is chosen from hydrogen, C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and -COR₄ wherein R₄ is chosen from C₁₋₅alkyl, C₁₋₅alkoxy, arylC₀₋₅alkyl and amino which is optionally independently or di-substituted by C₁₋₅alkyl, and arylC₀₋₅alkyl.

17. The compound according to claim 16 wherein W is CH, C-CH₃ or N.

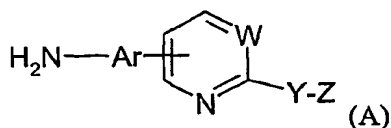
20

18. The compound according to claim 17 wherein the compound is chosen from:



25

19. A process of making the compounds of formula(A):



wherein Ar and W are as defined in claim 1;

5 and wherein for the formula(A):

Y is -CH₂-; and

Z is chosen from:

10 heterocycle chosen from morpholinyl, thiomorpholinyl, piperidinyl and pyrrolidinyl
each of the aforementioned Z are optionally substituted with one to three halogen, C₁₋₆
alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxy-carbonyl, aroyl, C₁₋₃ acyl, oxo,
pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl,
nitrile, phenyl wherein the phenyl ring is optionally substituted with one to two halogen,
15 C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m wherein the phenyl
ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy or di-(C₁₋₃
alkyl)amino;

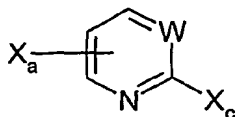
or Z is optionally substituted with one to three amino or amino-C₁₋₃ alkyl
20 wherein the N atom is optionally independently di-substituted by amino-C₁₋₆alkyl, C₁₋₃
alkyl, aryl-C₀₋₃alkyl, C₁₋₅ alkoxy-C₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃ acyl, C₁₋₃alkyl-S(O)_m-
or aryl-C₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino
group is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
or Z is optionally substituted with one to three aryl or heterocycle as hereinabove
25 described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or
C₁₋₆ alkoxy;

or Z is amino wherein the N atom is optionally independently mono- or di-substituted by
C₁₋₆alkyl or C₁₋₃alkoxy-C₁₋₃alkyl, C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy, nitrile-C₁₋

alkyl, C₁₋₆ alkyl-S(O)_m, aryl chosen from phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl each aryl being optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or nitrile, and phenyl-S(O)_m, wherein the phenyl ring is
 5 optionally substituted with one to two halogen, C₁₋₆ alkoxy or mono- or di-(C₁₋₃ alkyl)amino;

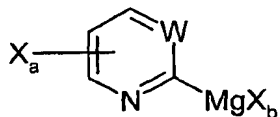
said reaction comprising:

10 i) reacting a compound of the formula(C)



(C)

with a magnesium reagent of the formula R-MgX_b; said reaction taking place in a suitable aprotic solvent at -78 °C to RT, for a reaction time of ½ hour to 2 hours producing the Grignard compound (F):



15

(F);

wherein

X_a is chosen from Br and Cl, and X_a is attached to the ring via the 4 or 5 position;

X_b is chosen from Br, Cl and I;

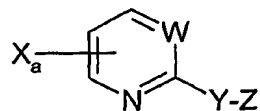
20 X_c is chosen from I and Br;

and

R is chosen from aryl, C₁₋₆alkyl and C₅₋₇cycloalkyl;

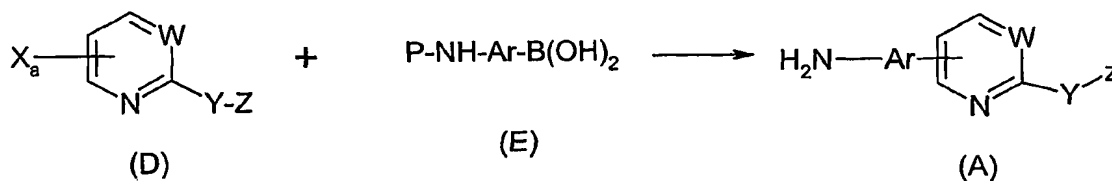
ii) subsequently reacting the Grignard compound(F) from the prior step with a *N,N*-
 25 dialkylformamide to form an aldehyde, and isolating the aldehyde;

iii) reacting the aldehyde in step ii) with an appropriate Z group under acid conditions in



a suitable solvent to provide the compound(D): (D) ;

- 5 reacting the compound of the formula(D) with an aryl boronic acid of the formula (E) and a palladium catalyst, in the presence of an appropriate ligand, in a suitable solvent at 0 °C to 150 °C, for about 1 to 24 hours:



10

wherein P in the formula(E) is an amino protecting group, and subsequently removing said protecting group under suitable conditions to produce a compound of the formula(A).

- 15 20. The process according to claim 19 wherein W is CH or N.

21. The process according to claim 20 wherein

- 20 in step i):

X_a is Br and attached at the 5 ring position;

X_c is I;

W is CH;

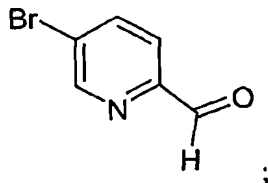
R is C₁₋₆alkyl;

25

in step ii):

the *N,N*-dialkylformamide is DMF;

the aldehyde is:



5

in step iii):

the acidic conditions use an acid chosen from HCl, AcOH, H₂SO₄;

the solvent is chosen from THF, methylene chloride, 1,2-dichloroethane;

the time is about 2 h at about RT followed by in situ reduction for about 2 h.

10

22. The process according to claim 21 wherein:

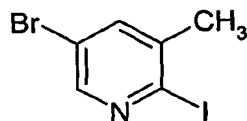
in step i) R is isopropyl; and

15

in step iii) the acid is AcOH; and the solvent is 1,2-dichloroethane.

23. A compound of the formula:

20



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/15665

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/38 C07D213/61

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>YANG Y ET AL: "SYNTHESIS OF 5-ARYLATED INDOLES VIA PALLADIUM-CATALYZED CROSS-COUPPLING REACTION OF 5-INDOLYLBORONIC ACID WITH ARYL AND HETEROARYL HALIDES" HETEROCYCLES, XX, XX, vol. 34, no. 7, 1992, pages 1395-1398, XP002036319 ISSN: 0385-5414 scheme 1 examples 8,11</p> <p style="text-align: center;">— — — — — — / —</p>	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

27 September 2001

Date of mailing of the international search report

10/10/2001

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Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/15665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HARGREAVES S L ET AL: "The synthesis of substituted pyridylpyrimidine fungicides using palladium-catalysed cross-coupling reactions" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 10, March 2000 (2000-03), pages 1653-1656, XP004189815 ISSN: 0040-4039 scheme 2 example 6; table 1 ----	1,13
A	DONGWEI C ET AL: "A Study of the Lithiation of 2,6-Dibromopyridine with Butyllithium, and its Application to Synthesis of L-739,010" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 15, 8 April 1996 (1996-04-08), pages 2537-2540, XP004029730 ISSN: 0040-4039 example 1 ----	19
A	WO 98 52558 A (CHEN JINSHAN ;PAULSEN HOLGER (DE); RANGES GERALD (US); RENICK JOEL) 26 November 1998 (1998-11-26) cited in the application claim 1 ----	1
A,P	WO 00 55139 A (BOEHRINGER INGELHEIM PHARMA) 21 September 2000 (2000-09-21) cited in the application examples 3,4,11,13,14,16,17,19 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/15665

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9852558	A	26-11-1998	AU 7585498 A DE 1019040 T1 EP 1019040 A1 ES 2151467 T1 WO 9852558 A1	11-12-1998 08-02-2001 19-07-2000 01-01-2001 26-11-1998
WO 0055139	A	21-09-2000	AU 2881700 A WO 0055139 A2	04-10-2000 21-09-2000